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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/719,553	11/20/2003	Hans Henrik Ipsen	04305/100E144-US2	3430

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DARBY & DARBY P.C.
P.O. BOX 770
Church Street Station
New York, NY 10008-0770

EXAMINER	
ROONEY, NORA MAUREEN	
ART UNIT	**PAPER NUMBER**
1644	

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10/31/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/719,553	IPSEN ET AL.	
	Examiner	Art Unit	
	Nora M. Rooney	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36-96* is/are pending in the application.

4a) Of the above claim(s) *44-65 and 74-96* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-43, 66-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed on 08/08/2007 is acknowledged.

2. Claims 36- 96 are pending.

3. Claims 44-65 and 74-96 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

4. Claims 36-43 and 66-73 are currently under examination as they read upon a recombinant mutant Bet v 1 allergen and the 'Triple-patch' mutant of species of 'ix.' in claim 37.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 36-43 and 66-73 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-22, 25-26, 28, 35, 37-39, 64 and 66-85 of copending Application No. 10/001,245. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims arrive at similar allergenic variants, and by what appears to the Examiner to be the same method of selection, or if not, by an obvious variant thereof. Specifically, Claims 1-22, 25-26, 28, 35, 37-39, 64 and 66-85 teach a mutant Bet V1 allergen with 1 or more substitutions, wherein said substitutions occur at many amino acid residues that are identical positions between the '245 application and the instant application, such as those recited in copending claim 22 and instant claim 37. Claim 22 of the '245 application recites substituting unspecified amino acids at one or more given positions, whereas the instant application recites specific substitutions at some of the same positions. However, on page 29 of the '245 specification in example 2595, the identical 'triple patch' mutant species of instant claim 37 is disclosed. Therefore, the claims are not

patentably distinct from one another for the same reasons as set forth in the Office Action mailed on 02/08/2007.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant's arguments submitted on 08/08/2007 have been fully considered, but are not found persuasive.

Applicant argues that this rejection should be held in abeyance until a Patent issues from one of the applications.

It is the Examiner's position that the rejection stands until the rejected claims are cancelled or until a terminal disclaimer is filed.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 36, 38-43 and 66-73 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of a recombinant mutant allergen from birch pollen major allergen Bet v a of SEQ ID NO:37 having the amino acid substitutions recited in claim 37.

However, applicant is not in possession of: a recombinant mutant Bet v 1 allergen derived from a naturally-occurring Bet v 1 allergen from the order Fagales, said recombinant mutant Bet v 1 allergen having: (a) a substitution of **a solvent-accessible amino acid residue that is conserved among Bet v 1 homologous allergens within the order Fagales**, said substitution occurring in **a B-cell epitope of said naturally-occurring Bet v 1 allergen**; (b) reduced specific IgE binding compared to said naturally-occurring Bet v 1 allergen from which it is derived; and (c) **an α-carbon backbone tertiary structure that is preserved as compared to the α-carbon backbone tertiary structure of said naturally-occurring Bet v 1 allergen** of claim 36; wherein said **solvent accessible conserved amino acid residue has a solvent accessibility of at least 20%** of claim 38; wherein **said conserved solvent-accessible amino acid residue is conserved with more than 70% identity among Bet v 1 homologous allergens within the taxonomic order from which said naturally-occurring Bet v 1 allergen originates** of claim 39; wherein the specific IgE binding of said mutant Bet v 1 allergen compared to said naturally-occurring Bet v 1 allergen from which it is derived is reduced by at least 5% of claim 40; wherein **the average root mean square deviation of the atomic coordinates comparing the α-carbon backbone tertiary structures of said recombinant mutant Bet v 1 allergen and**

said naturally-occurring Bet v 1 allergens is less than 2 Å in claim 41; wherein **said conserved solvent-accessible amino acid residue is within a patch of conserved amino acid residues connected over at least 400 Å of the surface of said naturally-occurring Bet v 1 allergen**; wherein said **solvent-accessible amino acid residue that is conserved among Bet v 1 homologous allergens within the taxonomic order from which said naturally-occurring Bet v 1 allergen is substituted with an amino acid that is not conserved among Bet v 1 homologous allergens within the taxonomic order from which said naturally occurring Bet v 1 allergen occurs**; or a recombinant mutant allergen derived from a naturally-occurring allergen within the order Fagales that is **homologous to Bet v 1 allergen**, said recombinant mutant allergens having: (a) **a substitution of a solvent-accessible amino acid residue that is covered among homologous allergens within the taxonomic order Fagales**, said **substitution occurring in a B-cell epitope of said naturally-occurring allergen**; (b) reduced specific IgE binding compared to said naturally-occurring allergen; and (c) **an α-carbon backbone tertiary structure that is preserved as compared to the α-carbon backbone tertiary structure of said naturally-occurring allergen** of claim 66; wherein said allergens homologous to Bet v 1 have an amino sequence that yields a BLAST probability of less than .1 when compared to an amino acid sequence of SEQ ID NO:37 of claim 67; wherein **said solvent-accessible conserved amino acid residue has a solvent accessibility of at least 20%** of claim 68; wherein **said conserved solvent-accessible amino acid residue is conserved with more than 70% identity among homologous allergens within the taxonomic order from which said naturally-occurring allergen originates** of claim 69; wherein the specific IgE binding of said mutant allergen compared to said naturally occurring allergen from which it is derived is reduced by at least 5%

of claim 70; wherein **the average root mean square deviation of the atomic coordinates comparing the α-carbon backbone tertiary structures of said recombinant mutant allergens and said naturally-occurring allergen is less than 2 Å** of claim 71; wherein **said conserved solvent-accessible amino acid residue is within a patch of conserved amino acid residues connected over at least 400 $Å^2$ of the surface of said naturally-occurring allergen** of claim 72; or wherein **said solvent-accessible amino acid residue that is conserved among homologous allergens within the taxonomic order from which said naturally-occurring allergen occurs** for the same reasons as set forth in the Office Action mailed on 02/08/2007.

Applicant's arguments submitted on 08/08/2007 have been fully considered, but are not found persuasive.

> Applicant argues: "The rejection is traversed on the grounds that the specification provides sufficient relevant identifying characteristics coupled with sufficient examples to demonstrate that that the inventors were in possession of the claimed invention at the time the application was filed.
>
> The specification provides adequate written description for claims 36, 38-43 and 66- 73. The written description requirement requires that the specification provide disclosure that allows one of ordinary skill in the art of the invention to "recognize that [the inventor] invented what is claimed." *Lockwood v. American Airlines, Inc.,* 107 F.3d 1565, 1572 (Fed. Cir. 1997); *see also Vas-Cath Inc. v. Mahurkar,* 935 F.2d 1555, 1563-64 (Fed. Cir. 1991) (Applicant "must convey with reasonable clarity to those skilled in the art that ... he or she was in possession *of the invention.")* (emphasis in original). The written description requirement "ensure[s] that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as detailed in the patent specification." *Reiffin v. Microsoft Corp.,* 214 F.3d 1342, 1354 (Fed. Cir. 2000). The written description requirement is met by providing sufficient structural, physical and/or functional properties that describe a genus and/or a sufficient members of genus that show the inventors were in possession of the claimed invention. *Regents of the University of California v. Eli Lilly & Co.,* 119 F.3d 1559, 1567-68 (Fed. Cir. 1997). Functional language may provide adequate written description "if in the

knowledge of the art the disclosed function is sufficiently correlated with a particular, known structure." *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1332 (Fed. Cir. 2003) *citing Enzo Biochem, Inc. v. Gen- Probe, Inc.*, 296 F.3d 1316, 1324 (Fed. Cir. 2002).

The instant application sets forth the invention of claims 36, 38-43 and 66-73 in sufficient detail to show that Applicants were in possession of the claimed invention. The claims are drawn to recombinant *Bet v 1* allergens from the order *Fagales (see* claim 36) and mutant allergens derived from naturally-occurring allergens within the order *Fagales* that are homologous to *Bet v 1 (See* claim 66) having a substitution of a solvent-accessible amino acid residue that is conserved among *Bet v 1* allergens from the order *Fagales* in a B-cell epitope of the allergen, and which has reduced IgE binding compared to the naturally-occurring *Bet v I* allergen from which it is derived and which has an et-carbon backbone tertiary structure that is preserved compared to the α- carbon backbone tertiary structure of the naturally occurring allergen.

The specification provides adequate written description sufficient to show that the inventors had possession of any such mutant *Bet v 1* allergens from the order *Fagales* or mutant allergens derived from a naturally-occurring allergen within the order *Fagales* that is homologous to *Bet v 1.* Hence, the specification discloses the existence of dominant IgE binding epitopes that are proposed to be constituted by tertiary structure dependent coherent surface areas large enough to accommodate antibody binding, and which are conserved among homologous allergens from related species. Specification at page 13, lines 11-18. The specification discloses that the amino acids to be mutated are found in a patch of conserved amino acid residues being coherently connected over at least 400 Å on the surface of the three dimensional surface of the allergen as defined by having a solvent accessibility of at least 20%. Specification at, e.g., page 20, lines 9-20. The specification further sets cut that homology among homologous proteins within a taxonomical order may be used to identify amino acids for substitution. Specification at page 35, lines 6-34. Further criteria to identify preferred amino acids for substitution are set forth on pages 20, line 31 through page 21, line 2 (preferentially select amino acids among most water soluble, near center of conserved patch and substitute polar amino acid with another polar amino acid and non-polar amino acid with another non-polar amino acid.) Thus, the specification describes the structural features of the amino acid substitution that are to be substituted on any allergen.

The specification further gives additional details on the structural features of *Bet v 1* and related proteins that further show possession of the invention of claims 36-43 and 66-73. Thus, at the time the application was filed, the structural basis for allergic *Bet v I* cross reactivity had been reported to be associated with three patches on the molecular surface of *Bet v 1.* Specification at page 24, line 34 through page 25, line 2. Amino acids within these patches that may be substituted were identified by aligning 122 sequences homologous to SEQ ID NO: 37, of which 57 sequences originated from taxonomically related species. Specification at page 26, lines 1-14. The specification at page 29, line 5-

12 further identifies amino acid substitutions in *Bet v 1* (SEQ ID NO: 37) (Thr10Pro, Asp25Gly, Asn28Thr, Lys32Gln, Glu45Ser, Asn47Ser, Lys55Asn, Thr77Ala, Pro108Gly) that may be used to make recombinant mutant allergens with single mutations or multiple mutations (Asn28Thr + Lys32Gln and "triple patch" mutant Glu45Ser, Asn28Thr + Lys32Gln, Pro108Gly). Thus, the specification gives particular structural features and examples that demonstrate possession of any recombinant *Bet v 1* allergen, as called for in the claims.

Moreover, as disclosed in the specification, proteins within the order *Fagales* that are homologous to SEQ ID NO: 37 are highly conserved in sequence and structure. The features used to identify amino acid substitutions to be made in *Bet v 1* of SEQ ID NO: 37 are thus also sufficient to show possession of mutant allergens of any *Bet v 1* homologous protein within the order *Fagales*. Related allergens are cross-reactive, allergic patients often react to several closely related species, and homologous allergens inhibit binding of IgE to each other. Specification at page 13, lines 18- 36. Thus, the structural features that define an IgE epitope are conserved among *Bet v 1* homologous proteins. Moreover, *Bet v 1* of SEQ ID NO: 37 shows about 90% amino acid identity with major allergens from pollens within the *Fagales* order and birch pollen allergic patients often show clinical symptoms of allergic cross-reactivity with *Bet v 1* homologous proteins from *Fagales* species. Specification at page 24, lines 8-14.

In setting forth the instant rejection, the Examiner cites *Eli Lilly, supra.* The nature of the instant invention and the disclosure of the instant specification, however, are very different from *Eli Lilly. In Eli Lilly,* the Federal Circuit held that the disclosure of the sequence of a rat insulin cDNA did not provide adequate written description for the insulin cDNA sequence of every vertebrate. *Eli Lilly* at 1566-67. *In Eli Lilly,* however, the specification failed to provide any features that described the claimed vertebrate insulin cDNA. The Court found that the claimed cDNA were described solely by their function or how to obtain them. The instant case is inapposite to *Eli Lilly. In* Eli Lilly the claims were directed to unknown cDNA sequences. The instant claims, by contrast, are drawn to mutant allergens that are derived by making substitutions in a family of allergens, i.e., *Bet v 1* homologous proteins from the order *Fagales,* with closely related sequences. *In Eli Lilly,* no structural features were provided that correlated with the function of the claimed vertebrate insulin cDNA. In the instant case, the specification provides that substituted amino acids are those amino acids that are conserved, solvent accessible amino acids that are part of IgE epitopes and that, in turn, IgE epitopes of *Bet v 1* homologous proteins are found within three patches on the surface of *Bet v 1* proteins. Accordingly, the written description requirement is satisfied in the instant case because the "in the knowledge of the art the disclosed function [i.e., IgE binding] is sufficiently correlated to a particular, known structure [i.e., conserved, solvent accessible amino acids present in coherently connected patches on the surface of *Bet v 1* homologous allergens]." *See Amgen, Inc.* at 1332, *discussing Enzo Biochem, Inc.* at 1324.

Nor does the decision of the Board of Patent Appeals and Interferences in *ex parte Kubin* (83 U.S.P.Q.2d 1410 (BPAI 2007)) support a finding that the instant specification fails to provide adequate written description for the pending claims. *In Kubin,* the Board upheld the rejection of a claim directed to isolated polynucleotides encoding polypeptides that (1) "are at least 80% identical to amino acids 22-221 of SEQ ID NO: 2" (i.e., the amino acid sequence for the extracellular domain of the protein natural killer cell activation inducing ligand ("NAIL") lacking the NAIL signal sequence) and (2) which bind to the glycoprotein CD 48. *Id.* at 1417. The specification in *Kubin* disclosed the sequence of two nucleic acids within the scope of the claim and three fusion proteins whose nucleic acid sequences would fall within the scope of the claim. *Id.* None of these sequences varied amino acids 22-221 ofSEQ ID NO: 2. *Id.*

The Board in *Kubin* found that the Applicant had failed to describe what domains of within amino acids 22-221 of SEQ ID NO: 2 correlated with the function of binding CD 48, and thus the Applicant had not described which NAIL amino acids could be varied and still maintain CD 48 binding. *Id.* Citing *Eli Lilly,* the Board found that in the absence of a structure-function correlation, the claim merely defined the invention by function, which was not sufficient to satisfy the written description requirement.

Kubin is distinguished from the instant case for much the same reasons as *Eli Lilly. In Kubin,* the Applicant failed to provide any features of amino acids 22-221 of SEQ ID NO: 2 that correlated with binding to CD 48. As set forth above, the instant specification, in contrast, sets forth structural features that allow one of ordinary skill in the art to identify amino acids in *Bet v 1* homologous proteins that contribute to IgE binding and thus may be mutated to obtain mutant allergens with reduced IgE binding. Furthermore, whereas in *Kubin* the Applicant failed to disclose any polynucleotides encoding NAIL protein that varied in amino acids 22-221, the instant applications identifies amino acid substitutions in *Bet v 1* (SEQ ID NO: 37) (Thrl0Pro, Asp25Gly, Asn28Thr, Lys32Gln, Glu45Ser, Asn47Ser, Lys55Asn, Thr77Ala, Prol08Gly) that may be used to make recombinant mutant allergens with single mutations or multiple mutations (Asn28Thr + Lys32Gln and "triple patch" mutant Glu45Ser, Asn28Thr + Lys32Gln, Prol08Gly) in which a conserved, solvent accessible amino acid in *Bet v 1* is substituted such that the mutant recombinant allergen derived thereby exhibits reduced IgE binding and retains the native ct-carbon backbone structure of *Bet v 1.* Moreover, each of the mutants tested (Glu45Ser; Prol08Gly; Asn28Thr + Lys32Gln; Glu45Ser, Asn28Thr + Lys32Gln, Pro 108Gly) had the properties called for in the instant claims. Thus, the instant application provides working examples for recombinant *Bet v 1* allergens with mutations in conserved, solvent accessible amino acids in patches on the surface of *Bet v 1* with reduced IgE binding and which retain a native ct-carbon backbone structure, whereas the Applicant in *Kubin* failed to provide any working examples of polynucleotides encoding a polypeptide at least 80% identical to amino acids 22-221 of SEQ ID NO: 2 and which bind CD 48.

> In short, as with *Eli Lilly,* the Applicant in *Kubin* failed to provide any structural features that correlated with the function of the polypeptide called for in the claim, whereas the instant specification sets out the features of *Bet v 1* homologous proteins that correlate with the function of IgE binding that is called for in the claim and which allow one of ordinary skill in the mutant art to make recombinant allergens with reduced IgE binding but which retain a native backbone structure. Thus, the basis of the Board's decision in *Kubin* does not apply to the instant claims.
>
> For at least all of the reasons set forth above, the specification provides adequate written description for the full breadth of the instantly claimed invention."

It is the Examiner's position that the specification does not disclose a correlation structure of the allergen and function (reduced specific IgE binding) and in this case functional limitations ("occurring in a B-cell epitope" and "α-carbon backbone tertiary structure that is preserved" of claim 36 "wherein said solvent accessible conserved amino acid residue has a solvent accessibility of at least 20%" of claim 38; "wherein the specific IgE binding of said mutant Bet v 1 allergen compared to said naturally-occurring Bet v 1 allergen from which it is derived is reduced by at least 5%" of claim 40; "wherein the average root mean square deviation of the atomic coordinates comparing the α-carbon backbone tertiary structures of said recombinant mutant Bet v 1 allergen and said naturally-occurring Bet v 1 allergens is less than 2 Å" in claim 41; "wherein said conserved solvent-accessible amino acid residue is within a patch of conserved amino acid residues connected over at least 400 Å of the surface of said naturally-occurring Bet v 1 allergen" of claim 42; "an amino sequence that yields a BLAST probability of less than .1 when compared to an amino acid sequence of SEQ ID NO:37" of claim 67; "wherein said solvent-accessible conserved amino acid residue has a solvent accessibility of at least 20%" of claim 68; "wherein the specific IgE binding of said mutant allergen compared to said naturally occurring allergen from which it is derived is reduced by at least 5%" of claim 70; "wherein the

average root mean square deviation of the atomic coordinates comparing the α-carbon backbone tertiary structures of said recombinant mutant allergens and said naturally-occurring allergen is less than 2 Å" of claim 71; "wherein said conserved solvent-accessible amino acid residue is within a patch of conserved amino acid residues connected over at least 400 $Å^2$ of the surface of said naturally-occurring allergen" of claim 72) such that a skilled artisan would have known what modification to make to the Bet v 1 allergens to attain the claimed function and functional limitations. "Possession may not be shown by merely describing how to obtain possession of member of the claimed genus or how to identify their common structural features" In re Kubin, of record, at page 16. In this instant case Applicants have not provided any guidance as to what mutation or combination of mutations will result in the claimed functions and functional limitations. "Without a correlation between structure and function, the claim does little more than define the claimed invention by function" *supra*, at page 17.

Applicant's argument that the instant specification, sets forth structural features that allow one of ordinary skill in the art to identify amino acids in *Bet v 1* homologous proteins that contribute to IgE binding and thus may be mutated to obtain mutant allergens with reduced IgE binding is not sufficient. The specification must also set forth the structureal features that allow one of ordinary skill in the are to produce Bet v 1 mutants substitutions occurring in a B-cell epitope and have α-carbon backbone tertiary structure that is preservedin addition to "wherein said solvent accessible conserved amino acid residue has a solvent accessibility of at least 20%" of claim 38; "wherein the specific IgE binding of said mutant Bet v 1 allergen compared to said

naturally-occurring Bet v 1 allergen from which it is derived is reduced by at least 5%" of claim 40; "wherein the average root mean square deviation of the atomic coordinates comparing the α-carbon backbone tertiary structures of said recombinant mutant Bet v 1 allergen and said naturally-occurring Bet v 1 allergens is less than 2 Å" in claim 41; "wherein said conserved solvent-accessible amino acid residue is within a patch of conserved amino acid residues connected over at least 400 Å of the surface of said naturally-occurring Bet v 1 allergen" of claim 42; "an amino sequence that yields a BLAST probability of less than .1 when compared to an amino acid sequence of SEQ ID NO:37" of claim 67; "wherein said solvent-accessible conserved amino acid residue has a solvent accessibility of at least 20%" of claim 68; "wherein the specific IgE binding of said mutant allergen compared to said naturally occurring allergen from which it is derived is reduced by at least 5%" of claim 70; "wherein the average root mean square deviation of the atomic coordinates comparing the α-carbon backbone tertiary structures of said recombinant mutant allergens and said naturally-occurring allergen is less than 2 Å" of claim 71; "wherein said conserved solvent-accessible amino acid residue is within a patch of conserved amino acid residues connected over at least 400 $Å^2$ of the surface of said naturally-occurring allergen" of claim 72. The instant applications identifies amino acid substitutions in *Bet v 1* (SEQ ID NO: 37) (Thrl0Pro, Asp25Gly, Asn28Thr, Lys32Gln, Glu45Ser, Asn47Ser, Lys55Asn, Thr77Ala, Prol08Gly) that may be used to make recombinant mutant allergens with single mutations or multiple mutations (Asn28Thr + Lys32Gln and "triple patch" mutant Glu45Ser, Asn28Thr + Lys32Gln, Prol08Gly) in which a conserved, solvent accessible amino acid in *Bet v 1* is substituted such that the mutant recombinant allergen derived thereby exhibits reduced IgE binding and retains the native ct-carbon backbone structure of *Bet v 1.* Moreover,

each of the mutants tested (Glu45Ser; Prol08Gly; Asn28Thr + Lys32Gln; Glu45Ser, Asn28Thr + Lys32Gln, Pro 108Gly) had the properties called for in the instant claims, but there is no guidance on other mutant Bet v 1 allergens with these properties. The working examples for recombinant *Bet v 1* allergens with mutations in conserved, solvent accessible amino acids in patches on the surface of *Bet v 1* with reduced IgE binding and which retain a native ct-carbon backbone structure are not sufficient support for the genes of all recombinant mutant Bet v 1 allergens encompassed by the claimed invention. In the instant case, definition by function does not suffice to define the genus because it is only an indication of what the allergen does and what functional properties it has, rather than what it is.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nora M. Rooney whose telephone number is (571) 272-9937. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571)

272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

October 29, 2007

Nora M. Rooney, M.S., J.D.

Patent Examiner

Technology Center 1600

Maher M. Haddad

MAHER M. HADDAD
PRIMARY EXAMINER